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DRUG SYNYHESIS

PRELIMINARY EVALUATION OF ANTICONVULSANT ACTIVITY OF SOME AROXYACETAMIDES AND AROXYETHYLAMINES

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Abstract: A series of aroxyacetamides and aroxyethylamines were prepared and evaluated for anticonvulsant activity in the maximal electroshock seizure (MES) and subcutaneous pentylenetetrazole seizure threshold (ScMet) assays and for neurotoxicity (TOX). Most of them exhibited anticonvulsant activity in the MES screen (mice, *i.p.*) in the doses up to 300 mg/kg b.w. The most active compound was **XVI**, which given in the dose 100 mg/kg b.w. produced 100% anticonvulsant protection after 0.5 h without neurotoxicity. The most promising compound in the VIa phase (rats, *p.o.*) was **VIII**, which produced higher anticonvulsant protection (to 75% at 0.5 h).

Keywords: aroxyacetamides, aroxyethylamines, anticonvulsant activity

Epilepsy is a disease that influences many aspects of life. It may be accompanied by other syndromes such as migraine or depression. The patient is often excluded from the society either due to epilepsy resistant to pharmacological treatment – which concerns 20-30% of all patients – or due to toxicity of drugs which must be taken for a long period of time. In spite of large progress in epilepsy treatment, recently developed drugs exhibit significant side effects such as ataxia, dizziness, sleepiness, double vision, cerebellum atrophy, nausea, vomiting (1-6), and hirsutism (7). Epilepsy itself, as well as the necessity for its continuous treatment, causes serious effects concerning physical, behavioral, cognitive and/or psychosocial aspects of life. Drug interactions are significant in this case. The situation of patients such as children or women during pregnancy is also difficult (6). Therefore, there exist premises for intensive research in the field of anticonvulsant substances free of side effects.

Searching for compounds with potential anticonvulsant activity we noticed that several N-acyl derivatives of the respective amines (8-11) and/or aminoacids (12-15) showed anticonvulsant properties in several models of seizures. Several drugs of this class are either used in therapy or being examined [e.g. ameltolide (16), levetiracetam (17), and remacemide (18)]. In previous studies we reported anticonvulsant properties of some aminoalkanolic or alkanolamide derivatives which displayed protection against maximal electroshock (MES) induced seizures, low neurotoxicity (TOX) and little protection in subcutaneous pentylenetetrazole induced seizures (ScMet) (11, 19). Some of them, i.e. *S*-(+)-2-N-[(2,6-dimethyl)-phenoxyethyl]-amino-1-butanol (11) and 2-[4-(benzyloxy)-benzoyl)]-2-N-methylamino-1-ethanol (19), potently prevent maximal electroshock seizures in mice, with an ED_{50} of 7.57 mg/kg b.w. and 51.8 mg/kg b.w., respectively. The protective indexes (PI=4.55 and 2.54, respectively) in the MES test in mice are higher than that of valproate (PI=1.7) and for the isomer *S* it is similar to that of carbamazepine (PI=4.9) (20).

The research results within the group of aminoalkanols or alkanolamides (11, 19) suggest that anticonvulsant activity within this group is related to the aminoalkanol configuration as well as electron structure of the substituents in the aromatic ring.

The presented results deal with preliminary pharmacological studies on the expected anticonvulsant activity of some appropriate (4-chlor-3-methylphenoxy)-acetylaminoalkanols [**I**-**VI**], (4-chlor-3-methylphenoxy)-acetylaminocyclohexane [**VI**), (2-chlor-5-methylphenoxy)-acetylaminoalkanols [**VIII**-**X**] and their amine analogues [**XI**-**XVII**]. Compounds **I**-**XVII** were evaluated for their anticonvulsant activity in the MES and ScMet seizures screens as well as for neurotoxicity.

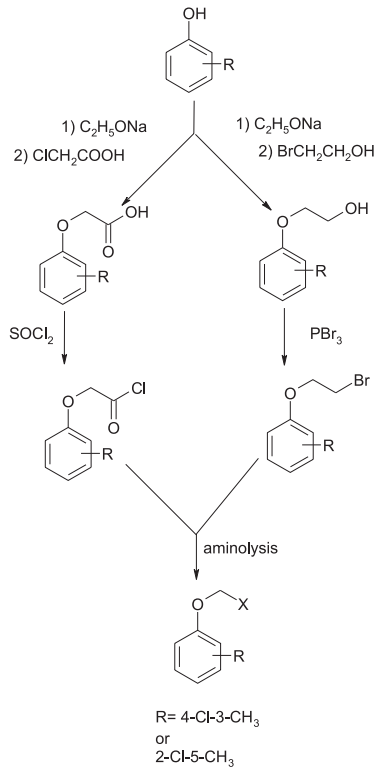
Chemistry

Appropriate aroxyacetamides [**I**-**X**] and aroxyethylamines [**XI**-**XVII**] were readily prepared according to the procedure shown in Scheme 1.

Compounds **I**-**X** were obtained through N-acylation of appropriate aminoalkanols (except for **VI**, where aminocyclohexane was used), using (4-chlor-3-methylphenoxy)- [**I**-**VII**] or (2-chlor-5-methylphenoxy)-acetyl chloride [**VIII-X**]. Two-phase system (H_2O / toluene) and stoichiometric amounts of K_2CO_3 as a HCl trapping agent were used. Compounds **XI**-**XVII** were obtained by N-alkylation of appropriate aminoalkanols using (4-chlor-3-methylphenoxy)- [**XI**-**XIV**] or (2-chlor-5-methylphenoxy)-ethyl bromide [**XV**-**XVII**]. The reaction was performed in the presence of K_2CO_3 in toluene solution. The yield of alkylation was in the range of 65 – 70%. Appropriate phenoxyacetyl chlorides and phenoxyethyl bromides were obtained according to the well known procedures as described previously (11, 21-22).

Some amines were converted into hydrochlorides [**XI**-**XIV**] in ethyl acetate with an excess of EtOH saturated with HCl. The appropriate enantiomers were recrystallized to constant rotation value (**XII** and **XIII** from a mixture of ethyl acetate / EtOH (3:1, v/v) and the respective bases from n-heptane).

The purity was checked for all compounds using TLC and their structures were confirmed by spectral analyses (IR, ^{1}H NMR). The structures and the physical and spectral data of the obtained compounds **I**-**XVII** are presented in Tables 1 and 2, respectively.



Scheme 1. Synthesis of the tested compounds [**I**-**XVII**].

Pharmacology

Compounds **I**-**XVII** were evaluated in preliminary pharmacological testing according to the Antiepileptic Drug Development program (ADD) at the National Institute of Neurological Disorders and Stroke (NINDS, Bethesda, MD, U.S.A.). All of them completed phase I testing, which included: maximal electroshock-induced seizures (MES; mice, *i.p.*), subcutaneous pentylenetetrazol-induced seizures (ScMet; mice, *i.p.*), and neurological toxicity (TOX), which was measured by the rotorod test. The results are presented in Tables 3 and 4.

RESULTS AND DISCUSSION

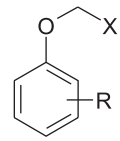
Among the tested amides **I**-**X** protective activity in the MES test in mice after *i.p.* administration was found for compounds **I**, **III**-**V**, **VII** and **X** in the dose 300 mg/kg b.w. at 0.5 h and for **IV** also at 4 h. Compound **IV** (isomer R), contrary to **III** (racemate) and **V** (isomer S) showed some activity in the ScMet screen and lower neurotoxicity at the dose of 300 mg/kg b.w.

From the group of compounds **XI**-**XVII** which are structural amine analogues of **I**-**X**, the best anticonvulsant activity for all of them in the MES test in mice, *i.p.* was observed at the dose of 100 mg/kg b.w. The most active compound was **XVI**, which given in the dose of 100 mg/kg b.w. produced 100% anticonvulsant protection after 0.5 h without neurotoxicity. When the pharmacological effects of the racemate [**XI**] and R and S enantiomers [**XII**, **XIII**] are compared, it seems that the racemate is the most promising. However, the racemate and R enantiomer had stronger activity (100% anticonvulsant activity at the dose of 100 mg/kg b.w. at 0.5 h) than S enantiomer, but R enantiomer was more toxic.

Table 4 shows data for compounds **I**, **VIII**, **XI**, and **XV**-**XVI** which were advanced to phase VIa according to the ADD program and were evaluated in rats after oral administration. In the MES test after *p.o.* administration of the dose of 30 mg/kg b.w. the anticonvulsant activity without neurotoxic effects was shown in all the tested compounds; the most promising compound was **VIII**, which produced higher anticonvulsant protection (to 75% at 0.5 h).

A replacement of appropriate amidoalkanol groups by aminoalkanol groups diminished anticonvulsant activity in rats in the MES screen.

Table 1. The structures and some physical data of the synthesized compounds (**I-XVII**).



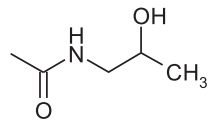
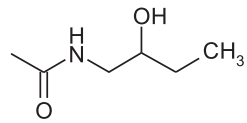
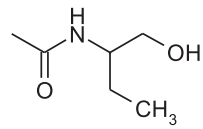
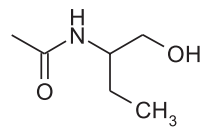
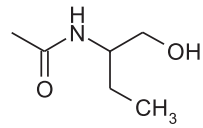
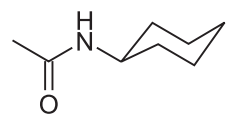
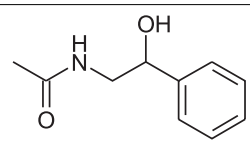
R	Compd.	X	Formula Molecular weight (M.w.) Melting point (M.p.) [°C] R_f $[\alpha]^{20}_{546}$	Log P_{comb}
4-Cl, 3-CH_3 for **I-VII**	**I**	 R,S	$C_{12}H_{16}NO_3Cl$ 257.71 67-69 0.46 [a)]	1.75
	II	 R,S	$C_{13}H_{18}NO_3Cl$ 271.74 100-102 0.53 [a)]	2.12
	III	 R,S	$C_{12}H_{18}NO_3Cl$ 259.73 96-98 0.52 [a)]	2.12
	IV	 R	$C_{12}H_{18}NO_3Cl$ 259.73 115-117 0.46 [a)] +24.0° ($CHCl_3$, c=2%)	2.12
	V	 S	$C_{12}H_{18}NO_3Cl$ 259.73 115-117 0.45 [a)]	2.12
	VI		-23.5° ($CHCl_3$, c=2%) $C_{15}H_{20}NO_2Cl$ 281.78 107-109 0.49 [b)]	3.98
	VII	 R,S	$C_{17}H_{18}NO_3Cl$ 319.79 143-145 0.55 [a)]	2.99

Table 1. (cont.)

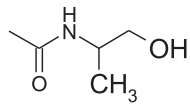
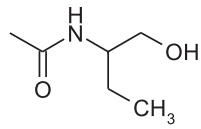
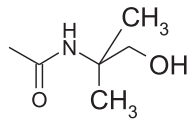
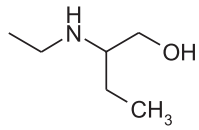
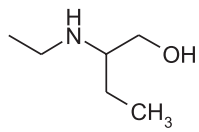
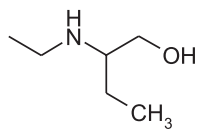
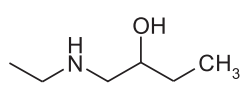
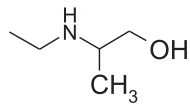
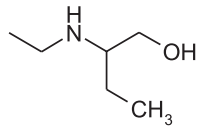
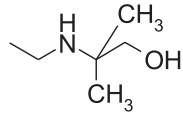
R	Compd.	X	Formula Molecular weight (M.w.) Melting point (M.p.) [°C] R_f $[\alpha]^{20}_{546}$	Log P_{comb}
2-Cl, 5-CH_3 for **VIII**-**X**	**VIII**	 R,S	$C_{12}H_{16}NO_3Cl$ 257.72 90-91 0.46 [a)]	1.75
	IX	 R,S	$C_{13}H_{18}NO_3Cl$ 271.75 71-72 0.53 [a)]	2.12
	X		$C_{13}H_{18}NO_3Cl$ 271.75 89-90 0.58 [a)]	2.44
4-Cl, 3-CH_3 for **XI**-**XIV**	**XI**	 x HCl R,S	$C_{13}H_{21}NO_2Cl_2$ 294.22 129-131 70-72 (base) 0.90 [c)]	2.62
	XII	 x HCl R	$C_{13}H_{21}NO_2Cl_2$ 294.22 145-147 48-50 (base) 0.88 [c)] -3.6° (CH_3OH, c=2%)	2.62
	XIII	 x HCl S	$C_{13}H_{21}NO_2Cl_2$ 294.22 145-147 48-50 (base) 0.89 [c)] +4.0° (CH_3OH, c=2%)	2.62
	XIV	 x HCl R,S	$C_{13}H_{21}NO_2Cl_2$ 294.22 159-161 69-71 (base) 0.85 [c)]	2.62

Table 1. (cont.)

R	Compd.	X	Formula Molecular weight (M.w.) Melting point (M.p.) [°C] R_f $[\alpha]^{20}_{546}$	Log P_{comb}
2-Cl, 5-CH_3 for **XV**-**XVII**	**XV**	 R,S	$C_{12}H_{18}NO_2Cl$ 243.74 82-84 0.43 [a)]	2.25
	XVI	 R,S	$C_{13}H_{20}NO_2Cl$ 257.76 64-65 0.47 [a)]	2.62
	XVII		$C_{13}H_{20}NO_2Cl$ 257.76 67-68 0.39 [a)]	3.11
	CBZ			3.30
	VA			2.61

[a)] toluene / acetone (1:1); [b)] toluene / methanol (5:1); [c)] ethanol / ethyl acetate (2:1)

Table 2. The IR and ^{1}H NMR spectral data of **I-III, VI-XI,** and **XIV-XVII.**

Compd.	IR (cm^{-1}) $\bar{\nu}$=OH and/or NH $\bar{\nu}$=C=O	δ [ppm], *J* [Hz]x
I	3397, 3321 1651	7.25 (d, *J*=8.7, 1H, H-5); 7.01 (bs, 1H, N-H); 6.80 (d, *J*=3.0, 1H, H-2); 6.68 (dd, *J*=8.7, *J*=3.0, 1H, H-6); 4.46 (s, 2H, $ArOCH_2$); 4.02-3.92 (m, 1H, C-H); 3.53 (ddd, *J*=13.9, *J*=6.6, *J*=3.2, 1H, NHCH); 3.20 (ddd, *J*=13.9, *J*=7.6, *J*=5.4, 1H, NHCH); 2.69 (bb, 1H, OH); 2.34 (s, 3H, CH_3Ar); 1.20 (d, *J*=6.3, 3H, CH_3)
II	3397, 3328 1646	7.24 (d, *J*=8.8, 1H, H-5); 7.04 (t, *J*=5.4, 1H, NH); 6.79 (d, *J*=3.1, 1H, H-2); 6.68 (dd, *J*=8.8, *J*=3.1, 1H, H-6); 4.45 (s, 2H, $ArOCH_2$); 3.70-3.63 (m, 1H, CH); 3.56 (ddd, *J*=13.8, *J*=6.6, *J*=3.1, 1H, NHCH); 3.22 (ddd, *J*=13.8, *J*=7.7, *J*=5.3, 1H, NHCH); 2.87 (bb, 1H, OH); 2.33 (s, 3H, CH_3Ar); 1.56-1.43 (m, 2H, CH_2); 0.97 (t, *J*=7.3, 3H, CH_3)
III	3402, 3327 1643	7.68 (d, *J*=8.7, 1H, NH); 7.31 (d, *J*=8.7, 1H, H-5); 6.97 (d, *J*=3.1, 1H, H-2); 6.81 (dd, *J*=8.7, *J*=3.1, 1H, H-6); 4.70 (t, *J*=5.6, 1H, OH); 4.50 (d, *J*=14.5, 1H, ArOHCH); 4.46 (d, *J*=14.5, 1H, ArOHCH); 3.74-3.65 (m, 1H, CH); 3.41-3.29 (m, 2H, CH_2OH); 2.28 (s, 3H, CH_3Ar); 1.62-1.52 (m, 1H, $HCHCH_3$); 1.40-1.29 (m, 1H, $HCHCH_3$); 0.81 (t, *J*=7.4, 3H, CH_3)
VI	3273 1657	7.25 (d, *J*=8.7, 1H, H-5); 6.81 (d, *J*=3.0, 1H, H-2); 6.69 (dd, *J*=8.8, *J*=3.0, 1H, H-6); 6.37 (d, *J*=7.0, 1H, N-H); 4.42 (s, 2H, $ArOCH_2$); 3.94-3.82 (m, 1H, CHN (cyclohexane)); 2.35 (s, 3H, CH_3Ar); 2.0-1.1 (m, 10H, (5xCH_2, cyclohexane))

Table 2. (cont.)

Compd.	IR (cm^{-1}) ν=OH and/or NH ν=C=O	δ [ppm], *J* [Hz]x
VII	3383, 3275 1639	7.95 (bb, 1H, N-H); 7.36 (s, 2H, H-Ar (Ph)); 7.35 (s, 2H, H-Ar (Ph)); 7.31 (d, *J*=8.8, 1H, H-5); 7.26 (s, 1H, H-Ar (Ph)); 6.78 (d, *J*=2.8, 1H, H-2); 6.60 (dd, *J*=8.8, *J*=2.8, 1H, H-6); 4.88 (dd, *J*=8.0, *J*=3.5, 1H, C-H); 4.49 (d, *J*=14.9, 1H, ArOHC<u>H</u>); 4.44 (d, *J*=14.9, 1H, ArO<u>H</u>CH); 3.78 (ddd, *J*=14.0, *J*=7.0, *J*=3.5, N<u>H</u>-CH); 3.45 (ddd, *J*=14.0, *J*=8.0, *J*=5.1, 1H, NHC<u>H</u>); 2.88 (bb, 1H, OH); 2.35 (s, 3H, CH_3Ar)
VIII	3391, 3329 1654	7.63 (d, *J*=8.3, 1H, NH); 7.29 (d, *J*=8.0, 1H, H-6); 6.90 (dd, *J*=1.9, *J*=0.8, 1H, H-3); 6.81 (ddd, *J*=8.0, *J*=1.9, *J*=0.8, 1H, H-4); 4.76 (t, *J*=5.5, 1H, OH); 4.57 (d, *J*=14.6, 1H, O-C<u>H</u>H-C=O); 4.53 (d, *J*=14.6, 1H, O-CH<u>H</u>-C=O); 3.91-3.82 (m, 1H, CH); 3.41-3.35 (m, 1H, C<u>H</u>HOH); 3.35-3.31 (m, 1H, CH<u>H</u>OH); 2.27 (t, *J*=0.8, 3H, CH_3Ar); 1.07 (d, *J*=6.7, 3H, CH_3-R)
IX	3404, 3253 1635	7.56 (d, *J*=8.5, 1H, NH); 7.29 (d, *J*=8.0, 1H, H-6); 6.89 (dd, *J*=1.8, *J*=0.8, 1H, H-3); 6.80 (ddd, *J*=8.0, *J*=1.8, *J*=0.8, 1H, H-4); 4.70 (t, *J*=5.6, 1H, OH, OH); 4.61 (d, *J*=14.6, 1H, O-C<u>H</u>-C=O); 3.72-3,66 (m, 1H, CH); 3.43-3.38 (m, 1H, CH<u>H</u>OH); 3.37-3.31 (m, 1H, CH<u>H</u>OH); 2.26 (t, *J*=0.8, 3H, CH_3Ar); 1.63-1.53 (m, 1H, C<u>H</u>H-Me); 1.42-1.32 (m, 1H, CH<u>H</u>-Me); 0.83 (t, *J*=7.4, 3H, R-CH_3)
X	3390, 3321 1654	7.30 (d, *J*=8.0, 1H, H-6); 7.28 (bs, 1H, NH); 6.92 (d, *J*=0.7, 1H, H-3); 6.81 (dd, *J*=8.0, *J*=0.7, 1H, H-4); 4.93 (t, *J*=5.6, 1H, OH); 4.50 (s, 2H, -O-CH_2-C=O); 3.40 (d, *J*=5.6, 2H, C<u>H</u>$_2$OH); 2.28 (s, 3H, $ArCH_3$); 1.25 (s, 6H, 2xCH_3)
XI **(base)**	3285, 3157	7.27 (d, *J*=8.8, 1H, H-5); 6.94 (d, *J*=3.0, 1H, H-2); 6.78 (dd, *J*=8.8, *J*=3.0, 1H, H-6); 4.44 (bs, 1H, OH); 4.03-3.95 (m, 2H, $ArOCH_2$); 3.40 (dd, *J*=10.5, *J*=4.9, 1H, C<u>H</u>H-OH); 3.27 (dd, *J*=10.5, *J*=6.4, 1H, CH<u>H</u>-OH); 2.88 (t, *J*=5.6, 2H, CH_2N); 2.47-2.41 (m, 1H, CH); 2.29 (s, 3H, Ar-CH_3); 1.75 (bs, 1H, NH); 1.40-1.33 (m, 2H, CH_2Et); 0.85 (t, *J*=7.4, 3H, CH_3Et)
XIV	3331, 2451 (NH^+)	7.27 (d, *J*=8.7, 1H, H-5); 6.94 (d, *J*=2.8, 1H, H-2); 6.79 (dd, *J*=8.7, *J*=2,8, 1H, H-6); 4.43 (bs, 1H, OH); 4.03-3.95 (m, 2H, $ArOCH_2$); 3.44-3.37 (m, 1H, CH); 2.86 (t, *J*=5.5, 2H, OCH_2CH$_2$N); 2.54 (dd, *J*=11.6, *J*=4.0, 1H, NHC<u>H</u>HCH); 2.44 (dd, *J*=11.6, *J*=7.7, 1H, NHCH<u>H</u>CH); 2.28 (s, 3H, CH_3Ar); 1.79 (bs, 1H, NH); 1.45-1.35 (m, 1H, C<u>H</u>HEt); 1.35-1.25 (m, 1H, CH<u>H</u>Et); 0.85 (t, *J*=7.4, 3H, CH_3Et)
XV	3290, 3157	7.26 (d, *J*=8.0, 1H, H-3); 6.98 (dd, *J*=8.0, *J*=2.0, 1H, H-6); 6.76 (ddd, *J*=8.0, *J*=2.0, *J*=0.8, 1H, H-4); 4.47 (t, 1H, OH); 4.12-4.02 (m, 2H, CH_2Oar); 3.32-3.27 (m, 1H, C<u>H</u>H-OH); 3.25-3.19 (m, 1H, CH<u>H</u>-OH); 2.96-2.86 (m, 2H, CH_2N); 2.71-2.64 (m, 1H, CH); 2.29 (dd, *J*=0.8, *J*=0.8, 3H, CH_3Ar); 1.85 (bs, 1H, NH); 0.93 (d, 3H, CH_3-C)
XVI	3288, 3138	7.26 (d, *J*=8.0, 1H, H-3); 6.98 (dd, *J*=1.9, *J*=0.6, 1H, H-6); 6.75 (ddd, *J*=8.0, *J*=1.9, *J*=0.8, 1H, H-4); 4.45 (t, *J*=5.3, 1H, OH); 4.10-4.03 (m, 2H, CH_2OAr); 3.32-3.27 (m, 1H, C<u>H</u>H-OH); 3.25-3.19 (m, 1H, CH<u>H</u>-OH); 2.96-2.86 (m, 2H, CH_2N); 2.71-2.64 (m, 1H, CH); 2.29 (dd, *J*=0.8, *J*=0.8, 3H, CH_3Ar); 1.79 (bs, 1H, NH); 1.44-1.28 (2H, CH_2Et); 0.93 (t, *J*=7.5, 3H, CH_3Et)
XVII	3274, 3106	7.25 (d, *J*=8.0, 1H, H-3); 6.97 (dd, *J*=1.9, *J*=0.7, 1H, H-6); 6.75 (ddd, *J*=8.0, *J*=1.9, *J*=0.7, 1H, H-4); 4.48 (t, *J*=5.3, 1H, OH); 4.03 (t, *J*=5.8, 2H, CH_2OAr); 3.18 (d, *J*=5.3, 2H, CH_2OH); 2.84 (t, *J*=5.8, 2H, CH_2N); 2.28 (dd, *J*=0.8, *J*=0.8, 3H, CH_3Ar); 1.66 (bs, 1H, NH); 0.96 (s, 6H, CH_3R)

Table 3. Anticonvulsant activity of the tested compounds (mice, *i.p.*) [**I**-**XVII**].

Compd.	Dose	MES[a]		ScMet[a]		Neurotoxicity[b]	
	mg/kg b.w.	0.5 h	4 h	0.5 h	4 h	0.5 h	4 h
I	30	–	–	–	–	–	–
	100	–	–	–	–	1/8	–
	300	1/1	–	–	–	3/4	–
II	30	–	–	–	–	–	–
	100	–	–	–	–	–	–
	300	–	–	–	–	3/4	–
III	30	–	–	–	–	–	–
	100	–	–	–	–	2/8	–
	300	1/1	–	–	–	3/4	–
IV	30	–	–	–	–	–	–
	100	–	–	–	–	–	–
	300	1/1	1/1	1/5	–	2/4	–
V	30	–	–	–	–	–	–
	100	–	–	–	–	1/8	–
	300	1/1	–	–	–	3/4	–
VI	30	–	–	–	–	–	–
	100	–	–	–	–	4/8	–
	300	–	–	–	–	3/4	–
VII	30	–	–	–	–	–	–
	100	–	–	–	–	–	–
	300	–	–	–	–	1/4	–
VIII	30	–	–	–	–	–	–
	100	–	–	–	–	–	–
	300	1/1	–	–	–	4/4	–
IX	30	–	–	–	–	–	–
	100	–	–	–	–	–	–
	300	–	–	–	–	4/4	–
X	30	–	–	–	–	–	–
	100	–	–	–	–	–	–
	300	1/1	–	–	–	2/4	–
XI	30	–	–	–	–	–	–
	100	3/3	–	–	–	3/8	–
	300	1/1	|	|	|	3/4	|
XII	30	–	–	–	–	–	–
	100	3/3	–	–	–	6/8	–
	300	|	|	|	|	4/4	|
XIII	30	–	–	–	–	–	–
	100	1/3	–	–	–	3/8	–
	300	|	|	|	|	4/4	|
XIV	30	–	–	–	–	–	–
	100	3/3	–	–	–	8/8	–
	300	|	|	|	|	4/4	|
XV	30	–	–	–	–	–	–
	100	2/3	–	–	–	2/8	–
	300	|	|	–	|	4/4	|
XVI	30	–	–	–	–	–	–
	100	3/3	–	–	–	–	–
	300	|	–	|	–	3/4	–
XVII	30	–	–	–	–	–	–
	100	2/3	–	–	–	4/8	–
	300	|	|	|	|	4/4	|

[a] No. animals protected / No. animals tested; [b] No. animals displaying motor impairment / No. animals used in the rotorod test; – the compound was either not active or not toxic in the particular case; | the compound was not tested in the particular case.

Table 4. Anticonvulsant activity of the compounds tested in phase VIa (rats, *p.o.*) [**I**, **VIII**, **XI**, **XV**, and **XVI**].

Compd.	Test	Dose	Time in hours				
		mg/kg	0.25	0.5	1.0	2.0	4.0
I	MES [a)]	30	1/4	-	2/4	1/4	-
	TOX [b)]	30	-	-	-	-	-
VIII	MES	30	-	-	-	-	-
	ScMet	50	1/4	3/4	-	2/4	1/4
	TOX	50	-	-	-	-	-
XI	MES	30	-	-	-	-	1/4
	TOX	30	-	-	-	-	-
XV	MES	30	-	-	1/4	-	-
	TOX	30	-	-	-	-	-
XVI	MES	30	1/4	-	-	1/4	-
	TOX	30	-	-	-	-	-

[a)] and [b)] see Table 3.

The calculated partition coefficient (logP) of the most anti-MES active compounds was within the range of 1.75-3.11 (Table 1) which corresponds to the calculated logP of valproate and carbamazepine (2.61 and 3.30, respectively).

EXPERIMENTAL

Chemistry

Melting points are uncorrected and determined using a Büchi SMP-20 apparatus. Analyses of C, H, N were within +/- 0.4% of the theoretical values. The IR spectra were recorded on a Jasco FT / IR 410 spectrometer. The ^{1}H NMR spectra were recorded on Bruker AMX spectrometer at 500.13 MHz in DMSO-d_6 using TMS as an internal standard. Analytical TLC was performed on precoated plates (silica gel, 60 F-254 Merck) using the solvent system toluene / acetone (1:1, v/v) [**I**-**V** and **VII**-**XVII**], toluene / methanol (5:1, v/v) [**VI**], and ethanol / ethyl acetate (2:1, v/v) [**XI**-**XIV**]; spots were visualized with UV light. Measurements of optical rotation ($[a]_{546}$) were performed using Polamat A (Carl Zeiss, Jena). Enantiomeric 2-amino-1-butanols ($[\alpha]^{20}_{546}$: (*R*) = -11.25^o; (*S*) = +11.15^o) were obtained earliner (12). Other reagents and solvents were commercially available materials of reagent grade. The theoretical values of the partition coefficient (Log $P_{comb.}$) of the synthesized structures were calculated using PALLAS 3.1 program.

General procedure for synthesis of **I-X.**

A mixture of 0.01 mole of appropriate aminoalkanols [for **I-V** and **VII-X**] or aminocyclohexane [for **VI**] with 0.025 mole K_2CO_3 in 15 mL of water and 15 mL of toluene was cooled to 10-12^o C. After cooling a solution of 0.011 mole (4-chloro-3-methyl)- [for **I-VII**] or (2-chloro-5-methyl)-phenoxyacetyl chloride [for **VIII-X**] in 30 cm^3 of dry toluene was added with vigorous stirring at 10-12^o C for 0.5 h. Then the reaction mixture was heated and then left to cool down. The precipitated amides deposit was filtered off, stirred with a 10% solution of $NaHCO_3$, and after drying recrystallized from n-heptane.

General procedure for synthesis of XI-XVII.

0.01 mole of an appropriate aminoalkanol was added to a solution of 0.01 mole of (4-chloro-3-methyl)- [for **XI**-**XIV**] or (2-chloro-5-methyl)-phenoxyethyl bromide [for **XV**-**XVII**] in 30 mL of toluene and the reaction mixture was refluxed in the presence of 0.01 mole K_2CO_3 for 6 h. Inorganic salts were filtered off from the hot mixture and washed with hot toluene (5 mL). The solvent was distilled off from the filtrate under reduced pressure. After addition of n-heptane (for bases) or ethanol saturated with HCl (for hydrochlorides) to the residue, the mixture was refluxed and cooled. The crystals formed were collected by filtration and dried. Recrystallization from n-heptane (for bases) gave **XV**-**XVII** and from ethanol with small amount of acetone gave **XI**-**XIV**.

Pharmacology

Initial evaluations for anticonvulsant activity were performed within the ADD program Epilepsy Branch, National Institute of Neurological Disorders and Stroke, National Institute of Health, Bethesda, MD, USA. The evaluations of anticonvulsant activity included Phase I and VIa tests procedures. The

screens were performed either in male Carworth Farms no. 1 (CF 1) mice (18-25 g) or male Sprague-Dawley rats (100-150 g). In the phase I studies which deal with qualitative assay, all the compounds were tested for activity in the MES and ScMet tests as well as in the rotorod screen for TOX. The examined compounds were suspended in 0.5% aq. methylcellulose and then administered at three dosage levels (30, 100 and 300 mg/kg) with anticonvulsant activity observed 0.5 and 4 h after *i.p.* administration in mice. Phase VIa was a similar qualitative evaluation to the Phase I evaluation, but the test drug was examined for oral activity in the rats using the three screens noted previously. The details of these procedures were published earlier (2). The results of phases I and VIa tests are listed in Tables 3 and 4, respectively.

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